III. REMARKS

Claims 1-25 are pending in this application. By this Amendment, claims 1, 3, 4, 5, 22 and 24 have been amended. Claim 6 has been cancelled, without prejudice. Thus, claims 1-5 and 7-25 remain pending. Reconsideration in view of the above amendments and the following remarks is respectfully requested.

Applicants do not acquiesce in the correctness of the rejections or objections and reserve the right to present specific arguments regarding any rejected or objected-to claims not specifically addressed. Further, Applicants reserve the right to pursue the full scope of the subject matter of the claims in a subsequent patent application that claims priority to the instant application.

Objections to the Claims

Claims 3-5 were objected to in the Office Action for not containing a period at the end of each claim. Claims 3-5 have been amended herein to contain periods at the end of each claim. Withdrawal of objection is respectfully requested.

Rejections under 35 U.S.C. 112, First Paragraph

Claim 6 stands rejected under 35 U.S.C. 112, first paragraph for alleged lack of enablement. In particular, the Examiner alleged that "..Applicant has not adequately described how one skilled in the art could obtain crystals in said forms."

In the interest of expediting prosecution, and as claim 1 sufficiently covers crystals in all forms, claim 6 has been cancelled, thus rendering this rejection moot with respect to that claim. Withdrawal of rejection is respectfully requested.

Rejections under 35 U.S.C. 112, Second Paragraph

Claims 1, 2, 7, 8 and 22-25 stand rejected under 35 U.S.C. 112, second paragraph for alleged indefiniteness in recitation of the term, "X_{50}." In particular the

Examiner alleged, "[t]here is no definition of the term X_{50} value and therefore it cannot be determined what type of size range Applicant is claiming."

Applicants traverse this rejection and assert that X_{50} is defined in paragraph 6 of the specification as follows:

> The present invention provides an injectable depot formulation comprising crystals of iloperidone or its metabolite or a pharmaceutically acceptable salt, hydrate, solvate, polymorph and stereoisomer thereof, wherein ***the mean particle size (X_{50} value)*** of the crystals is from 1 to 200 microns.

Applicants assert that the term "mean particle size," when used in combination with specific numerical ranges as recited in the claims, is sufficiently definite for purposes of 35 U.S.C. 112(2). One of ordinary skill in the art would know the meaning of "mean particle size" as a statistical term. Withdrawal of rejection is respectfully requested.

Rejections under 35 U.S.C. 103(a)

Claims 1-2 and 6-25 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Mutlib, et al. and Margolin et al. (U.S. Publication No. 2002/0045582 A1). The Examiner asserts that it would be obvious to combine the mention of iloperidone as a potential oral therapeutic with the methods of Margolin et al., which the Examiner concedes are directed solely to crystal forms of biological macromolecules, to arrive at the instant claimed invention.

Applicants respectfully traverse this rejection. As acknowledged by the Examiner, Mutlib et al. does not disclose injectable iloperidone formulations or the excipients of the claimed invention. Rather Mutlib et al. is merely directed to a method of assaying plasma levels of iloperidone and its metabolites following oral administration in humans. Nowhere in Mutlib et al. are methods of making or using injectable depot formulations of iloperidone or its metabolites described.

Additionally, not all compounds suitable for use as a pharmaceutical composition are found in, or can be prepared in, a crystallized form. Further, Applicants assert that it was not predictable that the compound in crystalline form within the claimed size ranges

would have the properties described in the instant specification. Nothing in Mutlib et al. or in any of the other cited references lend to any such predictability. Applicants respectfully request that the Office explain its conclusion regarding the inherent crystallinity of the claimed compounds.

Margolin et al. does not cure that which is lacking from Mutlib et al., namely, an injectable depot formulation of iloperidone or its metabolites. As the Examiner concedes, the entire disclosure of Margolin et al. is clearly directed to the making and using of crystal forms of biological macromolecules (specifically, proteins and nucleic acids). The Examiner's sweeping assertion that "the general properties of crystals vs. amorphous forms would be expected to be the same for protein and small molecule crystals" is directly contrary to Margolin et al., which specifically teaches away from the suitability of its teachings for non-macromolecules. For example, paragraph 10 explicitly distinguishes the properties and traits of biological macromolecules from "conventional chemical entities, such as for example their size, conformation and amphiphilic nature." Nearly every subsequent paragraph in Margolin et al. explicitly limits the suitability of the disclosed methods to use in macromolecular protein therapeutics due to the particular properties of macromolecules compared to that of small molecules. See also, paragraphs 22-23 of Margolin et al., explaining, *inter alia* that "molecular weight has a profound effect on all properties of macromolecules..."

Applicants respectfully assert that the chemical, physical and pharmacological differences between "conventional chemical entities" (i.e., small molecule compounds such as iloperidone) have been generally recognized for decades. Thus the Examiner's premise that the methods of Margolin et al. for biological macromolecules could be combined with that of the mere mention in Mutlib et al. of iloperidone as a potential oral therapeutic is faulty. To the contrary, these cited references either alone or in combination would not provide any motivation to one of ordinary skill in the art to be

successful generally for small molecule entities, much less iloperidone in particular. Withdrawal of rejection of claims 1-2 and 6-25 is respectfully requested.

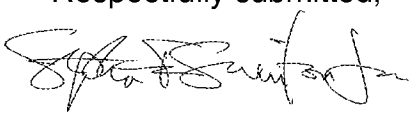
Claims 3-5 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Mutlib et al. and Margolin et al., in further view of Corey et al. The Examiner asserted that Corey et al. teaches enatioselective reduction of ketones and for that reason, cures the defects of Mutlib et al. of not disclosing enatioselective variations of iloperidone, or crystalline forms of iloperidone, or injectable formulations of iloperidone.

Applicants traverse this rejection. Corey et al. does not cure that which is lacking from Mutlib et al. and Margolin et al. as described above, namely an injectable formulation of iloperidone crystals or its metabolites wherein the crystals have an X_{50} value from 1-200 microns. Applicants note that not only does Mutlib et al. "not teach enantioselective variations of iloperidone...the cystalline form of the compound... [or] injectable iloperidone formulations," as conceded by the Office, but Mutlib et al. also fails to teach the use of either of the claimed enantiomers as a pharmaceutical composition.

Further, Corey et al. does not teach the claimed enantiomers, a crystalline form of iloperidone or its metabolites, an injectable formulation comprising iloperidone or its metabolites, or a pharmaceutical composition comprising iloperidone or its metabolites. Nothing in Corey et al. teaches or suggests that the disclosed method of enatioselective reduction of ketones generally would produce formulations of iloperidone enantiomers sufficiently pure that renders them suitable for injectable administration. Withdrawal of rejection is respectfully requested.

In view of the foregoing, Applicants respectfully request withdrawal of all rejections and allowance of the application. Should the Examiner require anything further from Applicants, the Examiner is invited to contact Applicants' undersigned representative at the number listed below.

Respectfully submitted,



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